COVER SHEET

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Forsythe ME, Crawford S, Sterling GJ, Whitehouse SL, Crawford R. Safeness of Simplex-tobramycin bone cement in patients with renal dysfunction undergoing total hip replacement:- *J Orthop Surg (Hong Kong) 2006;14(1):38-42*

The Safety Profile of Simplex-Tobramycin Bone Cement in THR in Patients With Renal Dysfunction

Running head: Safety profile of antibiotic cement in renal pts

ME Forsythe FRCSC
Research Fellow
Department of Orthopaedic Surgery*

GJ Sterling MBBS
Orthopadeic Registrar
Department of Orthopaedic Surgery
Royal Brisbane and Women's Hospital
Herston Road, Herston
Queensland 4029 AUSTRALIA

SL Whitehouse PhD
Research Fellow
Orthopaedic Research Unit
Queensland University of Technology*

S Crawford FRACS
Director of Orthopaedics
Department of Orthopaedic Surgery*

R Crawford D.Phil(Oxon)
Professor of Orthopaedic Research
Orthopaedic Research Unit
Queensland University of Technology*

* The Prince Charles Hospital, Rode Road, Chermside, Queensland 4032 AUSTRALIA

Work was conducted at The Prince Charles Hospital, Queensland. AUSTRALIA

Correspondence to: *Professor Ross Crawford*
Tel: +61 (0)7 3350 8481 *Fax: +61 (0)7 3350 8043*
E-mail: r.crawford@qut.edu.au

ABSTRACT

A prospective, consecutive series of six patients with renal dysfunction as defined by abnormal serum creatinine underwent cemented primary THR for osteoarthritis and the elution characteristics of Simplex-Tobramycin bone cement were compared to a previously reported group of nine patients with normal renal function. Blood, urine and drainage fluid specimens were collected for 72hours post-operatively. Very high concentrations of tobramycin were seen in the drainage fluid, with no significant difference between the two groups ($p<0.05$). Mean serum tobramycin levels peaked at 3hours, and declined rapidly to reach negligible levels at 72hours in both groups with no significant difference ($p<0.05$). Mean urinary tobramycin concentrations peaked at 12hours, with rapid decline by 48hours in both groups. Tobramycin was excreted significantly more slowly in the patients with renal dysfunction in the first 12hours ($p=0.05$), but not thereafter. Although serum creatinine levels were higher in the renal group throughout the study, neither group had a significant change at 72hours compared to their preoperative level. Excellent local delivery was achieved with minimal systemic concentrations in both groups and no change in preoperative renal function. Simplex-Tobramycin bone cement is an effective and safe means by which to deliver antibiotic following THR in patients with renal dysfunction.

KEY WORDS: Tobramycin; bone cement; pharmacokinetics, THR

INTRODUCTION

Antibiotic-laden acrylic bone cement has become popular as a prophylactic measure against the devastating complication of deep infection following total hip replacement. Its use in combination with systemic antibiotics has proven most effective[4,7]. Commercially available gentamicin-impregnated cement and Simplex antibiotic cement with erythromycin (500mg) and colistin (240mg) (Howmedica, Limerick, Ireland) have been widely available, and their safety and pharmacokinetic profiles are well documented[12,16]. Despite this, resistant strains of organism are providing renewed challenges in the management of infected total joint replacement[13].

Tobramycin may be a better antibiotic to admix with bone cement than currently available antibiotics. At levels achievable at the operative site with tobramycin-impregnated cement, all common gram negative and most gram positive organisms are susceptible, including organisms not susceptible with systemic administration[13]. Tobramycin is less ototoxic and nephrotoxic than gentamicin and has been proven to elute at higher concentrations than gentamicin from Palacos, Simplex and Zimmer cements[8,11]. Tobramycin has already been successfully used in several studies where it was added to Simplex P in the operating room[1,10,14]. Safe and effective bactericidal levels were swiftly established at the site of the implant, while serum concentrations were negligible after only 24 hours.

Problems associated with the addition of tobramycin to bone cement include weakening of the cement, generation of antibiotic-resistant bacteria and systemic toxicity. Tobramycin has been proven not to effect the mechanical characteristics of Simplex bone cement[2,6,9]. Clinically, the mixture of antibiotics to bone cement not only decreases infective loosening out to 14 years but also decreases the rate of aseptic loosening suggesting there are no clinical concerns with possible mechanical changes produced by the addition of antibiotics to cement[3]. Rates of systemic toxicity, in particular renal impairment with the use of antibiotic cement are almost nonexistent. In a prospective study, higher renal impairment rates were reported in patients treated with systemic dicloxicillin only (13%) as opposed to those treated with gentamycin impregnated cement only (0%) for prophylaxis during primary total hip replacement[5]. However, a recent case report documented acute renal failure after the use of a gentamycin impregnated spacer without any systemic antibiotics for a two stage revision total knee arthroplasty[17].

The pharmacokinetic profile of commercially prepared Simplex-Tobramycin bone cement has recently been published[15]. However, the safety of routine use of tobramycin has not been documented with commercially prepared Simplex-Tobramycin bone cement (Howmedica, Limerick, Ireland; 1 gram tobramycin sulphate; 40g powder, 20ml liquid) in patients with renal dysfunction. This study aims to compare the pharmacokinetic profile of tobramycin in blood, urine and at the operative site following the use of Simplex-Tobramycin bone cement in primary total hip replacement in patients with and without renal dysfunction.

MATERIALS AND METHODS

Six consecutive patients who had evidence of pre-existing renal dysfunction, as defined by abnormal pre-operative serum creatinine (males>0.12;females>0.1mg/l) were included in this study. This group of patients was compared to a previously reported group of nine patients with osteoarthritis with normal renal function who were selected prospectively for primary cemented total hip replacement. All patients with active infection, malignancy at the operative site and known sensitivity to aminoglycosides or acrylic bone cement were excluded from the study group. All patients received Keflin 1g, 6 hourly for 4 doses. Additional intravenous tobramycin was not used in these patients during the study period.

One mix of Simplex-Tobramycin bone cement for the acetabular component and two mixes for the femoral component were used in all cases. All drainage fluids and urine were collected for 48 hours after prosthesis implantation, divided into the time periods shown in Table 1. Venous blood samples were collected in parallel and up to 72 hours. Tobramycin concentrations were assayed on a Dimension RxL clinical chemistry system using a PETINIA method (Particle enhanced turbinometric inhibition immunoassay). The lower limit of detection for this assay is approximately 0.18 mg/l. Serum creatinine concentrations were also collected for each patient at the same time intervals and assays were also performed on the Dade Dimension RxL analyzer using a Jaffe reaction.

Statistical analysis was performed using parametric and non-parametric testing as dictated by the type of data collated, using SPSS statistical package (*SPSS Inc, Chicago, Illinois).* Where multiple testing was performed, Bonferroni's correction for multiple testing was utilized and the p-value for significance adjusted accordingly.

RESULTS

Patient demographics are presented for both groups in Table 2. Serum creatinine levels were significantly higher ($p = 0.001$) in the patients with renal dysfunction, but all other variables were similar between the two groups.

The data was tested for normality, which showed that other than the pre-operative variables, the data was non-parametric in nature. Hence, these means were compared using the t-test, whereas for all other variables, the groups were compared using the Mann-Whitney U-test.

Drainage fluid tobramycin assay levels are shown in Table 3. Comparison of the two groups indicated that there was no statistical difference between them at the 5% level.

The serum tobramycin levels for both groups are shown in Figure 1. Although the levels were higher at each time interval, there was no statistical difference between the groups at any of the time points.

The serum creatinine levels of both groups are shown in Figure 2. These were statistically significant at the 5% level at every time interval. Bonferroni's correction was applied at each time point.

Urinary excretion of tobramycin was maximal in the period 3 to 12 hours after insertion of the prosthesis in both groups, and these values were significantly different at the 5% level between the two groups ($p=0.012$ at 3 hours, $p=0.009$ at 12 hours). These were not significant at the other time points. Urinary tobramycin excretion is shown in Figure 3.

Correlation between the peak tobramycin and peak creatinine levels for each patient was performed. As this data was normally distributed, the Pearson correlation coefficient was calculated as -0.416 which was not significant statistically ($p=0.411$).

DISCUSSION

Tobramycin is an aminoglycoside closely related to gentamicin. At levels seen at the operative site, it has a similar spectrum of activity, but is slightly more active against *Pseudomonas* and is less ototoxic and nephrotoxic than gentamicin[11,13]. Its elution characteristics are superior to gentamicin[8]. It is therefore an attractive alternative as an additive to acrylic bone cement in the prevention of periprosthetic infection.

Studies have demonstrated very high local concentrations of tobramycin with minimal systemic absorption and no systemic side effects when using tobramycin powder mixed with cement in the operating suite[1,10,14]. Our study demonstrates effective and safe local delivery of tobramycin in patients with renal dysfunction by the commercially available Simplex-Tobramycin bone cement. Levels achieved at the operative site were similar in both groups and far in excess of the minimum inhibitory concentration for common pathogenic bacteria, even after 48 hours[6,9,11].

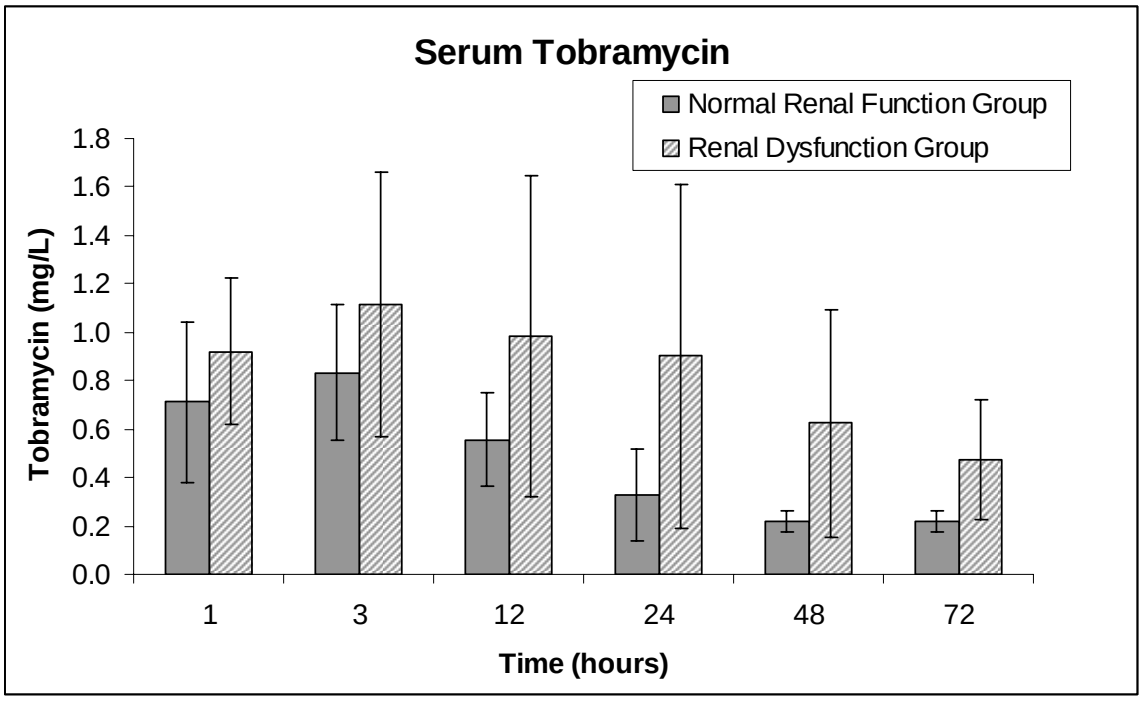
Systemic absorption was minimal in both groups. Both groups had their average peak tobramycin at 3 hours with a gradual decline to negligible levels at 72 hours. Although the renal group had higher systemic concentrations at all time periods, it was not significant. The average peak serum tobramycin levels for each group were below 2mg/L and the peak in any one patient was 2.1mg/L for one time interval only. Although sustained elevations above 2mg/L are not recommended, the threshold for nephrotoxicity is said to be 6.0-12.0 mg/L[9,11].

Serum creatinine was significantly higher in the renal group throughout the study with both groups dropping their average values at 3 hours with a gradual rise back to preoperative levels at 72 hours. This dip probably represents a fluid load from the perioperative period resulting in dilution and a drop in serum creatinine. At 72 hrs, no patients in either group had a significant rise from their preoperative levels.

Serum tobramycin was rapidly excreted in both groups in the first 12 hours with a gradual decline thereafter. It was not as rapidly excreted in the renal group because of the renal dysfunction and therefore the serum concentration remained higher for longer in this group. Patients in this study had moderate renal dysfunction, which is representative of a group of elective surgical candidates and is clinically relevant. It is hard to extrapolate this data to patients with severe renal dysfunction (dialysis); however, these patients may not be suitable for elective surgery. Furthermore, we did not find any correlation between peak serum tobramycin levels and creatinine, so it is probably safe in that population as well.

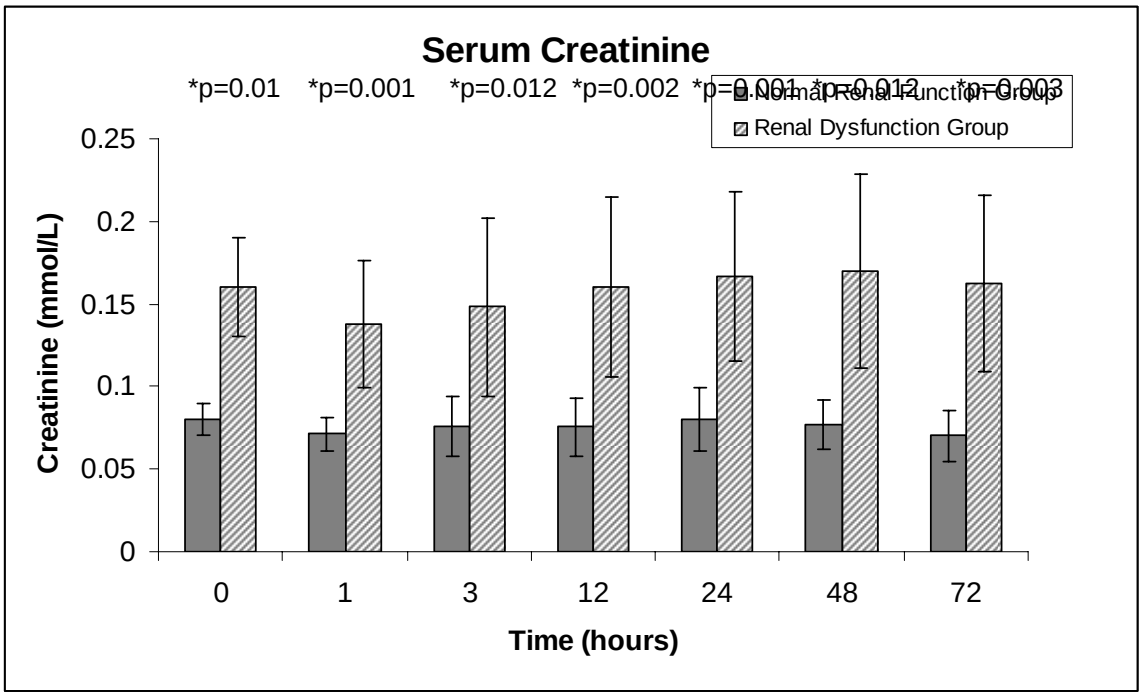
Simplex-Tobramycin bone cement delivers very high local bactericidal concentrations of tobramycin. Systemic absorption is minimal, with rapid renal excretion in patients with renal dysfunction. Based on this study, the pharmacokinetic profile of Simplex-Tobramycin bone cement appears to be appropriate for use in elective total hip replacement in patients with renal dysfunction.

Figure 1. Serum tobramycin levels at each time point.



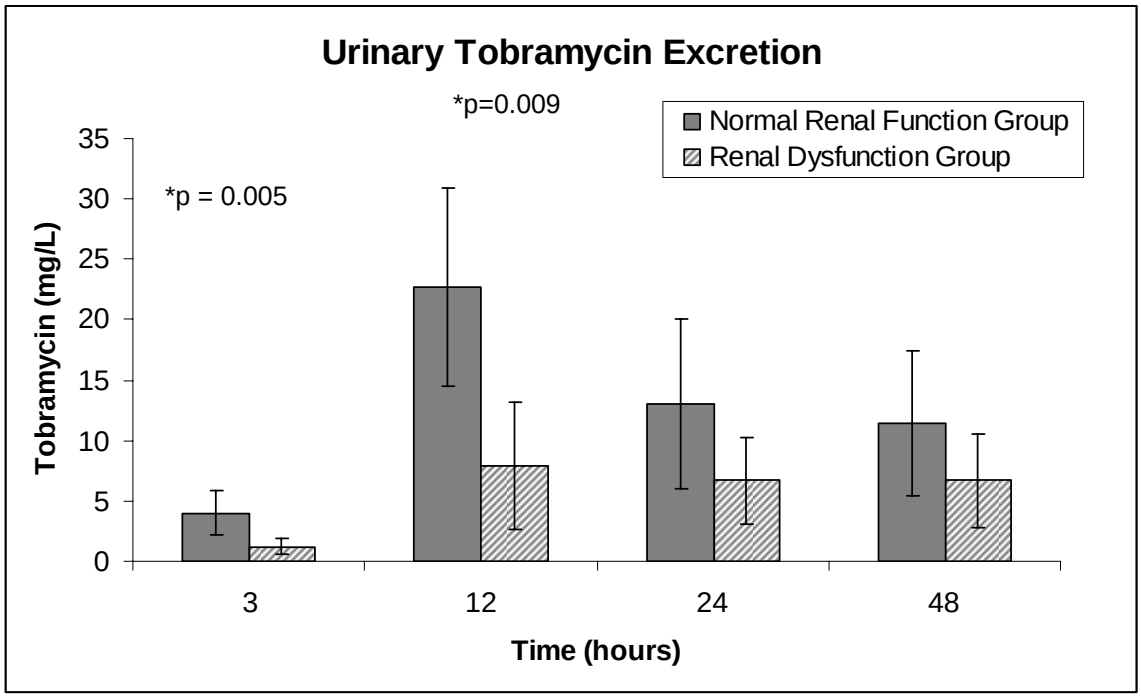
* significant at 5%
Error bars are ± standard deviation

Figure 2. Serum creatinine levels at each time point.



*significant at 5%
Time 0 = preoperative

Figure 3. Urinary excretion of tobramycin at each time point



* significant at 5%

Table 1: Timing of post-operative specimen collection.

Pharmacokinetic Evaluation	Pre-op	1 hour[ϰ]	3 hours	12 hours	24 hours	48 hours	72 hours
Blood	√	√	√	√	√	√	√
Wound Exudate		√	√		√	√	
Urine			√	√	√	√	

[ϰ] Time 0 is time of femoral insertion of cement.

Table 2. Patient demographics

Case Number	Group	Sex	Age	Height (cms)	Weight (kg)	Plasma creatinine
1	A	F	51	173	89	0.07
2	A	M	67	169	92	0.09
3	A	F	89	156	77	0.08
4	A	F	66	167	74	0.09
5	A	M	74	161	75	0.1
6	A	M	73	173	91	0.09
7	A	F	81	155	69	0.08
8	A	F	51	167	59	0.07
9	A	M	79	179	94	0.07
Mean (SD)	***n = 9***	***M/F 4/5***	***70.1 (12.9)***	***166.7 (8.1)***	***80.0 (12.1)***	***0.08* (0.01)***
10	B	F	83	158	59	0.16
11	B	M	77	182	97	0.21
12	B	F	49	164	63	0.11
13	B	M	76	166	75	0.18
14	B	F	67	152	70	0.15
15	B	M	62	172	75	0.17
Mean (SD)	***n = 6***	***M/F 3/3***	***69.0 (12.3)***	***165.7 (10.5)***	***73.2 (13.3)***	***0.16* (0.03)***

- **significant at 5% level**
- **Group A: normal renal function group**
- **Group B: renal dysfunction group**

Table 3. Mean (SD) for drainage tobramycin levels. P-values are those obtained when tested using Mann-Whitney U-test.

Time point	Normal renal function	Renal dysfunction	p-value
1 hour	103.0 (42.9)	90.3 (26.3)	0.727
3 hours	70.9 (40.3)	71.5 (21.3)	0.689
24 hours	37.3 (13.9)	39.0 (11.4)	0.864
48 hours	15.8 (4.9)	20.8 (18.9)	0.683

*** significant at 5% level**

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